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Title: Validation of impedance cardiography in pulmonary arterial hypertension

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Short title: Impedance cardiography in PAH.

Abstract

Background: Noninvasive methods of measuring cardiac output are highly desirable in pulmonary arterial hypertension. We therefore sought to validate impedance cardiography (ICG) against thermodilution (TD) and cardiac magnetic resonance (CMR) in the measurement of cardiac output in patients under investigation for pulmonary arterial hypertension.

Methods: A prospective, cross-sectional study was performed to compare single-point measurements of cardiac output obtained by ICG (CO_{ICG}) technology (PhysioFlow®) with: a) contemporaneous TD measurements (CO_{TD}) at rest and steady-state exercise during right heart catheterisation and b) CMR measurements (CO_{CMR}) at rest obtained within 72 hours.

Results: Paired CO_{ICG} and CO_{TD} measurements were obtained in 25 subjects at rest and 16 subjects at exercise. CO_{CMR} measurements were obtained in 16 subjects at rest. There was unsatisfactory correlation and agreement between CO_{ICG} and CO_{TD} at rest ($r=0.42$, $p=0.035$; bias: 1.21 L/min, 95% CI: -2.33–4.75 L/min) and exercise ($r=.65$, $p=.007$; bias: 1.41 L/min; 95% CI: -3.99–6.81 L/min) and, in the change in CO_{ICG} and CO_{TD} from rest to exercise ($r=0.53$, $p=0.033$; bias: 0.76 L/min, 95% CI: -3.74–5.26 L/min). There was also a lack of correlation and unsatisfactory agreement between resting CO_{ICG} and CO_{CMR} ($r=0.38$, $p=0.1$; bias: 1.40 L/min, 95% CI: -2.48–5.28 L/min). In contrast, there was close correlation and agreement between resting CO_{TD} and CO_{CMR} ($r=0.87$, $p<0.001$; bias: -0.16 L/min, 95% CI: -1.97–1.65).

Conclusions: In a representative population of patients under investigation for

pulmonary arterial hypertension, ICG showed insufficient qualitative and quantitative value in the measurement of resting and exercise cardiac output when compared with TD and CMR.

Keywords: cardiac output; thermodilution; cardiac magnetic resonance

Introduction

Pulmonary arterial hypertension (PAH) is characterised by increased pulmonary vascular resistance resulting in progressing right ventricular failure, left ventricular underfilling and reduced cardiac output (Galiè et al. , 2015). Cardiac output and cardiac index either at baseline or following therapeutic interventions have been identified among the most robust indicators of right ventricular function and prognosis in PAH (Humbert et al. , 2010; McLaughlin et al. , 2002; D'Alonzo et al. , 1991). Accordingly, normalisation of cardiac index has become an important treatment goal endpoint in PAH (Galiè et al. , 2015, McLaughlin et al. , 2013;).

Thermodilution (TD) (Ganz et al. , 1971) remains the reference standard for the measurement of cardiac output in PAH; it is reliable, detects directional changes and correlates well with the Fick technique in patients with precapillary pulmonary hypertension even in the presence of low cardiac output and significant tricuspid regurgitation (Hoeper et al. , 1999). More recently, cardiac magnetic resonance (CMR) has offered a noninvasive method of assessment of the right ventricular function (Hundley et al. , 1995) and has been successfully validated against the Fick method in the measurement of cardiac output in PAH (Mauritz et al. , 2008). However, both TD and CMR have certain limitations. TD is invasive and subject to technical errors (Nishikawa and Dohi, 1993; Stevens et al. , 1985) whereas CMR is restricted by a number of factors including higher cost and limited availability, time-consuming analysis, incompatibility with infusion pumps and requirement of breath holding which may be difficult for patients (Peacock and Vonk Noordegraaf, 2013).

Impedance cardiography (ICG) relies on the principle that variations in the bioimpedance to an alternating current flow during cardiac ejection result in a specific waveform from which stroke volume can be calculated (Charloux et al. , 2000). ICG is attractive due to its potential for noninvasive measurements of cardiac output at rest and activity on a beat-to-beat basis (Bour and Kellett 2008; Tang and Tong, 2009); however, it has not been adequately validated in PAH to date. We therefore sought to investigate the qualitative and quantitative validity of ICG against TD and CMR in the measurement of resting and exercise cardiac output in patients under investigation for PAH.

Materials and Methods

Study design

A prospective, cross-sectional study was performed. All consecutive patients who underwent right heart catheterisation for investigation of PAH in the Scottish Pulmonary Vascular Unit between December 2014 and November 2015 were eligible. Approval from the West of Scotland Research Ethics Committee (14/WS/1075) and written consent were obtained.

Single-point measurements of cardiac output were obtained using ICG (CO_{ICG}) and compared with a) contemporaneous TD measurements (CO_{TD}) at rest and steady-state exercise during right heart catheterization and b) CMR measurements (CO_{CMR}) at rest obtained within 72 hours. All measurements were performed in a blinded fashion and all CO_{ICG} and CO_{CMR} measurements were performed by single operators (MP and GJ, respectively).

Measurements of CO_{ICG} and CO_{TD} at exercise were obtained in patients who consented

to exercise in the supine position during right heart catheterization. Subjects either performed straight leg raising or cycled on an electronically braked ergometer (Angio 917900, Lode B.V., Groningen, The Netherlands) secured to the catheterisation table. Cycling rate was maintained at 60 revolutions·min⁻¹ and workload kept constant matching 50% of patient's maximal oxygen uptake (VO₂max) measured the previous day during an upright cycle cardiopulmonary exercise test. In order to reach physiological steady state, measurements were obtained during the sixth minute of exercise.

Right heart catheterisation & Thermodilution

Diagnostic right heart catheterisation was performed according to current guidelines (Galiè et al. , 2015). A balloon-tipped, double-lumen, fluid directed 7 Fr Swan Ganz catheter was advanced through an 8F introducer sheath inserted into the right internal jugular vein. The positioning of the catheter was confirmed with the presence of pulmonary artery pressure waveform from its distal port and fluoroscopic visualisation of its distal tip in the pulmonary artery. Cardiac output was measured with the TD technique (Ganz et al. , 1971) following the injection of 10 mL sterile, ice-cold isotonic (0.9%) saline through the proximal (right atrial) lumen of the Swan–Ganz catheter. The drop in temperature was measured at the distal thermistor. The final value used was the average of 3 measurements agreeing within 10%.

Impedance Cardiography

CO_{ICG} measurements at rest and exercise were obtained using a commercially available technology (PhysioFlow®, Manatec Biomedical, Macheren, France), a detailed description of which can be found elsewhere (Charloux et al. , 2000; Richard et al. , 2001). In brief, PhysioFlow uses variations in the transthoracic impedance to a high-frequency (75 kHz),

low-amperage (1.8 mA) alternating current across the thorax during cardiac ejection to calculate stroke volume. Its basic equation for calculating stroke volume (Signal-Morphology-ICG™) has resulted from the introduction of a novel approach to impedance cardiography in order to overcome the confounding variables of basal thoracic impedance (including thorax morphology, fluid and gas content, blood resistivity and skin thickness) and inter-electrode distance. This is achieved by relying only on change in impedance (dZ) to establish stroke volume, independent of baseline impedance (Z_0) (Charloux et al. , 2000, Tan et al. , 2006, Tonelli et al. , 2011).

In the PhysioFlow algorithm, an initial evaluation of stroke volume index is computed at rest during 24 consecutive heart beats (autocalibration procedure) by using the largest impedance variation during systole ($Z_{\max} - Z_{\min}$), the largest rate of variation in the impedance signal (contractility index, $dZ/dt \max$), the thoracic fluid inversion time (time in ms between the start of the QRS complex and the first nadir after the peak of the ejection velocity on the first mathematical derivative; a surrogate of the left ventricular ejection time), heart rate, and pulse pressure (systolic minus diastolic arterial pressure). Cardiac output (l/min) is then calculated by multiplying the stroke volume index by body surface area and heart rate [R-R interval determined on the electrocardiographic (ECG) first derivative] (Bour and Kellett 2008, Charloux et al. , 2000, Tonelli et al. , 2011).

CO_{ICG} measurements required skin preparation with shaving, scraping and cleaning for the application of six transcutaneous electrodes (PhysioFlow PF50) and performed by a single investigator (MP) as instructed/trained by the manufacturer. Two emitting electrodes were applied at the left base of the neck, above the supraclavicular fossa and two sensing electrodes along the xiphoid. In the exercising patients, the two sensing electrodes were

positioned at the left paravertebral area, at the level of xiphoid. One electrode at the mid-sternum and one at the left lateral chest wall were used to provide a single electrocardiogram lead. Subjects' sex, age, height, weight and supine systolic and diastolic blood pressure were logged in the PhysioFlow software and autocalibration was initiated after a period of 5 minutes during which subjects remained still and relaxed on the catheterisation table. Signal quality was verified by visualizing the electrocardiographic tracing and its first derivative ($dECG/dt$) and the impedance waveform (ΔZ) and its first derivative (dZ/dt) (Charloux et al. , 2000) and approved by the manufacturer following manual review in a blinded fashion. CO_{ICG} measurements were obtained thereafter in 10-second intervals throughout right heart catheterisation and downloaded to a purpose-specific notebook computer (Lenovo, North York, Canada). Manual review of the data and artifact detection was performed retrospectively. Data thought to be physiologically implausible, i.e. stroke volume for a given subject greater than their mean stroke volume $\pm 20\%$ (at unchanged heart rate, i.e. variation ≤ 5 beats/min), were deleted from the series. The final value of CO_{ICG} was the average of all values obtained during TD series.

Cardiac magnetic resonance

Phase-contrast CMR was performed on a 1.5T MAGNETOM Avanto MRI scanner (Siemens, Munich, Germany) during simultaneous electrocardiogram recording and continuous breathing. A velocity-encoded, k-space-segmented, gradient-echo sequence was used to generate 30 matched pairs of phase and magnitude images (echo time/repetition time/flip angle/slice thickness/temporal resolution/image matrix/field of view/in-plane resolution/velocity encoding range: TE 2.18/TR 29.9/30°/5mm/dependent on heart rate/256×256/320mm×240mm/1.25mm×1.25mm/0-150cm.sec⁻¹). Retrospective

electrocardiogram gating was used to ensure complete cardiac cycle coverage. The average acquisition time was 2–3 minutes, depending on heart rate. Left ventricular stroke volume was measured 2–4 cm above the aortic valve and distal to the coronary arterial ostia (Mauritz et al. , 2008). Imaging analysis was performed using the Argus software (Siemens, Erlangen, Germany).

Statistical analysis

Data are presented as means \pm standard deviation (SD). Pearson correlation (r) was calculated as measures of raw associations between measurements. P values <0.05 were considered significant. The agreement between the three techniques was analysed in a pairwise manner using the Bland-Altman analysis (Bland and Altman 1986). All analyses were performed using the SPSS statistical software (v. 20, IBM SPSS Statistics, Chicago, IL).

Results

Patient characteristics

Twenty-eight patients were studied between November 2014 and December 2015. Due to failed PhysioFlow autocalibration in 3 patients, the final analysis included 25 patients all of whom had paired CO_{ICG} and CO_{TD} measurements at rest; 16 of those patients also had paired measurements of CO_{ICG} and CO_{TD} at exercise (5 patients performed straight leg raise and 11 patients cycled) and 16 had measurements of CO_{CMR} at rest within 72 hours.

Clinical and physiological patient characteristics are presented in Tables 1 and 2 and measurements of CO_{ICG} , CO_{TD} and CO_{CMR} in Table 3. None of the patients had significant cardiac shunt. Echocardiographic evidence of tricuspid valve regurgitation was present in

all patients: 14, trace to mild, 7 mild to moderate, and 3 moderate/severe to severe. Atrial fibrillation was present in 4 patients.

Impedance cardiography versus thermodilution

Correlation between CO_{ICG} and CO_{TD} was weak at rest ($r=0.42$, $p=0.035$) but improved at exercise ($r=0.65$, $p=0.007$) and when looking at changes from rest to exercise ($r=0.53$, $p=0.033$). Bland-Altman analysis of the resting measurements showed significant overestimation of cardiac output by ICG and wide limits of agreement compared with TD (bias: 1.21 L/min, 95% confidence interval (CI): -2.33–4.75 L/min). Although both ICG and TD detected an increase in cardiac output from rest to exercise in all cases, their agreement remained poor at exercise (bias: 1.41 L/min, 95% CI: -3.99–6.81 L/min) and changes in cardiac output from rest to exercise (bias: 0.76 L/min, 95% CI: -3.74–5.26 L/min) (Figure 1, Table 3).

Impedance cardiography versus cardiac magnetic resonance

There was no correlation between CO_{ICG} and CO_{CMR} ($p=0.1$) and the agreement between ICG and CMR was poor (bias: 1.40 L/min, 95% CI: -2.48–5.28 L/min) (Figure 1, Table 3).

Thermodilution versus cardiac magnetic resonance

There was a strong correlation ($r=0.87$, $p<0.01$) and good agreement between CO_{TD} and CO_{CMR} (bias: -0.16 L/min, 95% CI: -1.97–1.65) (Figure 1, Table 3).

All the above results remained essentially unchanged when the subset of PAH patients ($n=14$) was examined separately (data not shown).

Discussion

This study tested ICG against TD and CMR in the measurement of cardiac output in patients under investigation for pulmonary arterial hypertension. Whereas there was a close correlation and agreement between TD and CMR, ICG technology showed insufficient correlation and significant overestimation of cardiac output with at least twice as wide limits of agreement compared with TD and CMR. These findings apply for both rest and exercise conditions and the change from rest to exercise and did not change when the subset of PAH patients was examined separately.

A previous validation of the PhysioFlow technology against TD (Tonelli et al. , 2011) in 39 patients with suspected or known pulmonary hypertension of various aetiologies, showed stronger correlations for resting cardiac output ($r=0.94$) and considerably smaller bias (0.3 L/min) but still wide limits of agreement (-2.2 to 2.8 L/min). Elsewhere, relative changes in measurements of cardiac index by PhysioFlow during incremental exercise were able to help identify subjects with severe PAH but the incremental value of PhysioFlow over peak oxygen uptake was relatively modest and measurements were not possible in a quarter of patients (Ferreira et al. , 2012). Nonetheless, change in cardiac index measured by PhysioFlow has been associated with six-minute walk distance and heart rate recovery in 30 patients with pulmonary hypertension of various aetiologies (Tonelli et al. , 2013).

A different ICG device has shown strong correlation with Fick ($r=0.84$) and TD ($r=0.80$) in the measurement of resting cardiac output and strong agreement with both methods in the measurement of resting cardiac index in 39 subjects with precapillary pulmonary hypertension (bias: -0.13 L/min/m², 95% CI: -1.05 to 0.79 L/min/m² versus Fick; bias: -0.23 L/min/m², 95% CI: -1.49 to 0.63 L/min/m² versus TD) (Yung et al. , 2004). In another

study of 65 patients with precapillary pulmonary hypertension, whole-body ICG showed good correlation with TD ($r=0.715$) and Fick ($r=0.653$) and satisfactory agreement with both methods in the measurement of resting cardiac output (bias: 0.50, 95% CI: -1.61 to 2.61 L/min versus TD; bias: -0.54, 95% CI: -2.57 to 1.49 L/min versus Fick) (Taniguchi et al. , 2013). Finally, transthoracic bioimpedance cardiography, a similar technology to ICG, showed acceptable results versus TD ($r=0.60$, bias: -0.81, 95% CI: -3.54 - 1.92) and Fick ($r=0.54$, bias: 0.02, 95% CI: -2.41- 2.44) in the measurement of resting cardiac output in 50 patients with pulmonary hypertension of various aetiologies (Rich et al. ,2013). Therefore, previous evidence on the validity and reliability of ICG and similar technologies in precapillary pulmonary hypertension remains limited to small, individual studies with some encouraging but preliminary results.

The reasons behind the lack of accuracy of the ICG in the present population are not clear. As previously stated, the PhysioFlow algorithm should not be confounded by determinants of basal thoracic impedance such as thoracic morphology, fluid and gas content, perspiration, blood resistivity, skin and subcutaneous adiposity thickness and inter-electrode distance (Charloux et al. , 2000). However, motion artifacts induced by exercise and exaggerated ventilatory responses to exercise might have interfered with the ICG signal (Warburton et al. , 1999; Edmunds et al. , 1982). Furthermore, measurement of stroke volume in the PhysioFlow algorithm requires calculation of the ventricular ejection time through measurement of the ‘thoracic flow inversion time’ (Charloux et al. , 2000). The latter depends on the pulse pressure and heart rate which are typically pathological in PAH patients; this potential source of error can be amplified by dissociation between electrical and cardiac mechanical events in the lieu of higher pulmonary vascular pressures

(Ferreira et al. , 2012). Also, the main pulmonary artery in PAH becomes dilated and frequently exceeds the aortic diameter which might have introduced an overestimation of the largest impedance variation during systole ($Z_{\max}-Z_{\min}$) during the autocalibration procedure (Ferreira et al. , 2012). Finally, very low cardiac output, significant regurgitant volumes, hemodynamically significant cardiac shunts and cardiac arrhythmias may hamper ICG tracings (Bour and Kellett 2008) but mean cardiac in the present population was preserved and none of the patients had significant cardiac shunt. However, three patients had moderate/severe-to-severe tricuspid regurgitation and four had atrial fibrillation. Whether these factors had collectively accounted for the significant minority of patients with invalid ICG signal (3 out of 28 patients, 11 %) is unknown.

The present study is limited by the small and inhomogeneous population. However, the present population is well-representative of patients who undergo investigation for PAH in clinical practice. Also, CMR was not contemporaneous to ICG and TD but it was performed in a blinded fashion within as little as 72 hours to minimize the possibility of significant interval changes in cardiac output; this is supported by the good agreement between CMR and TD.

Conclusion

In a representative population of patients under investigation for pulmonary arterial hypertension, ICG technology showed insufficient correlation and significant overestimation of cardiac output with at least twice as wide limits of agreement compared with TD and CMR. These findings do not support the quantitative and qualitative validity of ICG in the current population. Further research is warranted to allow for the routine use of other ICG and similar technologies in the noninvasive assessment of central

haemodynamics in pulmonary arterial hypertension.

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Figure Legends

Figure 1: Bland–Altman plots comparing cardiac output measured by impedance cardiography (CO_{ICG}), thermodilution (CO_{TD}) and cardiac magnetic resonance (CO_{CMR}): a) CO_{ICG} versus CO_{TD} at rest; b) CO_{ICG} versus CO_{CMR} at rest; c) CO_{ICG} versus CO_{TD} at exercise; d) change in CO_{ICG} versus change in CO_{TD} from rest to exercise; 3) CO_{TD} versus CO_{CMR} at rest.

Table 1: Clinical patient characteristics¹.

Characteristic	ICG vs. TD at rest (n=25)	ICG vs. TD vs. CMR at rest (n=16)	ICG vs. TD at exercise (n=16)
Age, y	63.8 ± 11.9	59.6 ± 11.5	62.1 ± 12.3
Sex (male: female)	13: 12	8:8	8:8
BMI, kg/m^2	28.1 ± 5.5	28.4 ± 5.7	28.1 ± 5.3
WHO FC, <i>II:III:IV</i>	5: 17: 3	4: 11: 1	4: 12: 0
6MWD, <i>m</i>	268.3 ± 134.8	285.1 ± 140.2	325.9 ± 124.4
Diagnosis			
IPAH	7	5	4
CTD	5	3	4
PoPH	2	2	1
PH due to left heart disease	3	1	2
PH due to lung respiratory diseases and/or hypoxia	4	2	1
CTEPH	1	1	1
No PH	3	2	3

¹ Data are presented as means ± SD. ICG: impedance cardiography; TD: thermodilution; CMR: cardiac magnetic resonance; BMI: body mass index; WHO FC: World Health Organization functional class; 6MWT: six-minute walk distance; IPAH: idiopathic pulmonary arterial hypertension; CTD: connective tissue disease associated PAH; PoPH: portopulmonary arterial hypertension; PH: pulmonary hypertension; CTEPH: Chronic thromboembolic pulmonary hypertension.

Table 2: Physiological patient characteristics at right heart catheterisation².

Characteristic	ICG vs. TD at rest (n=25)	ICG vs. TD vs. CMR at rest (n=16)	ICG vs. TD at exercise (n=16)
mean PAP, <i>mm Hg</i>	35.3 ± 12.3	35.2 ± 12.4	Rest: 31.9 ± 10.9
			Exercise: 52.4 ± 17.6
PAOP, <i>mm Hg</i>	6.5 ± 5.2	6.8 ± 6.3	Rest: 5.5 ± 3.5
			Exercise: 11.6 ± 6.7
CO, <i>L/min</i>	4.7 ± 1.7	4.8 ± 1.9	Rest: 5.2 ± 1.8
			Exercise: 7.9 ± 3.1
CI, <i>L/min/m²</i>	2.5 ± 0.9	2.6 ± 1.0	Rest: 2.7 ± 0.9
			Exercise: 4.2 ± 1.6
PVR, <i>Wood units</i>	7.4 ± 6.2	7.3 ± 6.9	Rest: 5.7 ± 3.7
			Exercise: 5.6 ± 4.2

² Data are presented as means ± SD. PAP: pulmonary artery pressure; PAOP: pulmonary artery occlusion pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance.

Table 3: Numerical values, Pearson's correlation coefficient (r) and Bland–Altman analyses for cardiac output³.

	Modality (n)	Mean CO, <i>L/min</i>	Correlation coefficient (P value)	Bias, <i>L/min</i>	Lower and Upper Limits, <i>L/min</i>
CO _{ICG} vs. CO _{TD}	Rest (25)	5.93 ± 1.66 vs. 4.72 ± 1.70	r=0.42 (0.035)	1.21	-2.33 – 4.75
CO _{ICG} vs. CO _{CMR}	Rest (16)	6.40 ± 1.78 vs. 5.01 ± 1.77	r=0.38 (0.1)	1.40	-2.48 – 5.28
CO _{ICG} vs. CO _{TD}	Exercise (16)	9.31 ± 3.44 vs. 7.91 ± 3.07	r=0.65 (0.007)	1.41	-3.99 – 6.81
ΔCO _{ICG} vs. ΔCO _{TD}	Rest to exercise (16)	3.51 ± 2.69 vs. 2.75 ± 1.77	r=0.53 (0.033)	0.76	-3.74 – 5.26
CO _{TD} vs. CO _{CMR}	Rest (16)	4.85 ± 1.88 vs. 5.01 ± 1.77	r=0.87 (<0.001)	-0.16	-1.97 – 1.65

³ Data are presented as means ± standard deviation. CO: cardiac output; CO_{ICG}: impedance cardiography-measured cardiac output; CO_{TD}: thermodilution-measured cardiac output; CO_{CMR}: cardiac magnetic resonance imaging-measured cardiac output; ΔCO_{ICG} and ΔCO_{TD}: changes in CO_{ICG} and CO_{TD} from rest to exercise.

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